Relevance to Human Cancer of *N*-Nitroso Compounds,
Tobacco Smoke and Mycotoxins.
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LUNG CANCER AND THE CHANGING CIGARETTE

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Epidemiological studies have shown that the long-term smoker of low-yield cigarettes has a 20-50% lower risk of lung cancer than the smoker of high-yield cigarettes. This risk reduction is attributed to changes in the make-up of cigarettes and especially to the introduction of filter tips. Other changes relate to the use of tobaccos that produce lower smoke yields, including reconstituted and expanded tobaccos, as well as utilization of porous cigarette paper and perforated filter tips. New developments in the make-up of commercial cigarettes must be monitored in order to prevent unfavourable introductions. Although a smoke-free society should be the major public health goal, recent consumer statistics do not support this goal. Thus, a strong social case is made for further developments in the low-yield cigarette.

In 1961, Wynder and Day offered three postulates for the causation of noncommunicable diseases, including cancer:

(1) The greater and the more prolonged the exposure to the factor, the greater the risk of a population involved.

(2) The epidemiological pattern should be consistent with the distribution of the factor.

(3) Removal or reduction of the risk factors for a given population group should be followed by a reduction in the incidence of disease.

More than 100 epidemiological studies from various countries have demonstrated a dose-response relationship between the number of cigarettes smoked and the risk for cancer of the lung (IARC, 1986; US Department of Health and Human Services, 1989). Laboratory studies have substantiated these findings by documenting the dose-response relationship between exposure to cigarette smoke and tumours of the upper respiratory tract in hamsters (Dontenwill, 1974) and that between application of smoke condensate to the skin of mice and rabbits and tumour yield at the site of application (Wynder & Hoffmann, 1967). These findings clearly satisfy postulate (1) for a causative association between cigarette smoking and lung cancer.

Postulate (2) is sustained by the correlation between age at onset of cigarette smoking and depth of inhalation with risk for lung cancer. Further support is gleaned from the observation that, by comparison to cigarette smokers, primary cigar and pipe smokers have

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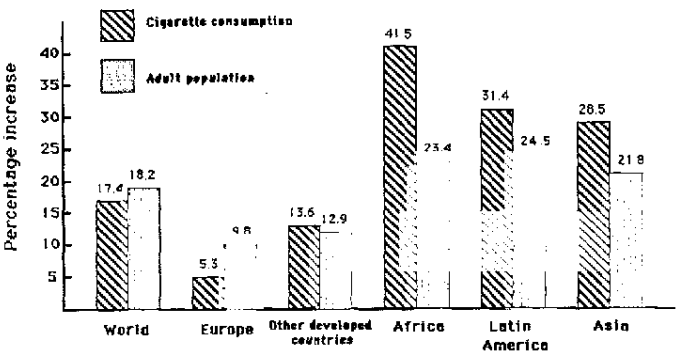
a lower risk for cancer of the lung but the same risk for cancer of the oral cavity (US Department of Health and Human Services, 1989).

The observed decrease in lung cancer risk upon cessation of cigarette smoking supports postulate (3) for cancer causation. More importantly, it also has major public health implications. Independent of the length of smoking history, the risk for tobacco-related diseases diminishes further as the period of abstention from smoking increases (Table 1). Thus, the demand for a smoke-free society by the year 2000 (Koop, 1986) deserves the full support of the medical and scientific community. Unfortunately, the recent statistics on tobacco use do not support this goal. Between 1971-75 and 1979-81, the percentage increase in cigarette consumption in all parts of the world, except Europe, exceeded the increase in population (Fig. 1).

Figure 1. Change in apparent cigarette consumption and adult population size, by region; 1971-75 to 1979-81[a]



[a] From World Health Organization (1986)

These data on cigarette consumption reinforce the need for health education about the harmful effects of cigarette smoking and for the widest availability of smoking cessation programmes. However, these figures also show that a strong case can be made for less toxic cigarettes, since far too many people seemingly cannot or will not give up the smoking habit.

The changing cigarette — epidemiological observations

Since the early epidemiological studies on the association of cigarette smoking and lung cancer clearly showed a dose-response relationship, product modification was seen as one possible approach to reducing exposure (Wynder & Hoffmann, 1962). Changes in the design of cigarettes, most notably use of filter tips but also alterations of the composition of cigarettes, were implemented in several countries in the late 1950s and early 1960s. Since then, the yields of smoke condensate ('tar') and of nicotine in the smoke stream have fallen drastically. For example, between 1960 and 1984, sales-weighted average 'tar' delivery of cigarettes in the USA, the UK and the Federal Republic of Germany decreased from 26, 31 and 25 mg to 14.2, 13.7 and 12.8 mg, respectively, that is, a reduction of 45-50%. During

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the same period, nicotine yields decreased by about 38-44% (Adlkofer *et al.*, 1988). As stated above, the introduction of filter tips was the first and most evident change in cigarette design, and more than 50% of smokers in North America and Europe were using filter cigarettes by 1965 (Weber, 1972). Most of the epidemiological assessments of lung cancer risk have therefore involved comparisons of statistics on smokers of plain cigarettes with those on long-term smokers of filter cigarettes (> 10 years).

The relative risks for lung cancer of smokers who switched to filter cigarettes in comparison with the risk for lung cancer of smokers of plain cigarettes are listed in Table 2. The reduction in risk in these studies varies from 20 to 50% depending on the type of cigarette smoked for the longest time, thus also supporting postulate (3). This observation appears to pertain primarily to a reduction in the Kreyberg I lung cancer type (including squamous-cell, large-cell and oat-cell lung carcinoma); reduction in Kreyberg II type of lung cancer appears to be limited to male smokers (Wynder & Kabat, 1988).

Table 1. Lung cancer mortality ratios in ex-cigarette smokers, by number of years since stopping smoking[a]

Study population	*Years since stopping smoking*	*Mortality ratio*	
British physicians	1-4	16.0	
	5-9	5.9	
	10-14	5.3	
	≥15	2.0	
	Current smokers	14.0	
US veterans	1-4	18.83	
	5-9	7.73	
	10-14	4.71	
	15-19	4.81	
	≥ 20	2.10	
	Current smokers	11.28	
Japanese males	1-4	4.65	
	5-9	2.50	
	≥ 10	1.35	
	Current smokers	3.79	
		Number of cigarettes smoked per day	
		1-19	≥ 20
US males aged 50-69	< 1	7.20	29.13
	1-4	4.60	12.00
	5-9	1.00	7.20
	≥ 10	0.40	1.06
	Current smokers	6.47	13.67

[a] From US Department of Health and Human Services (1982)

On the basis of the extent of sales-weighted 'tar' reduction in the smoke of filter cigarettes, an even greater decline in the risk for lung cancer might have been predicted. Two factors may explain why the reality differs from the expectation: (i) sales-weighted 'tar'

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and nicotine values are based on standardized machine-smoking of cigarettes, and (*ii*) most smokers of low-yield cigarettes compensate for the reduced nicotine delivery by smoking more, by drawing puffs more frequently and more intensely, and by inhaling more deeply (Herning *et al.*, 1981; Haley *et al.*, 1985; Augustine *et al.*, 1989).

Epidemiological studies have also reported a reduction in the risks for cancers of the larynx and urinary bladder for long-term smokers of filter cigarettes (Wynder & Stellman, 1979; Vineis *et al.*, 1984; Wynder *et al.*, 1988).

In addition to comparing the cancer risks of smokers of plain and filter cigarettes, epidemiological studies have been concerned with the relative risk of smoking black cigarettes *versus* blended or bright cigarettes. It was found that smokers of cigarettes made exclusively of black tobaccos, such as those that are commonly smoked in France, North Africa and Cuba, are at higher risk for cancers of the lung, larynx and urinary bladder than are smokers of blended or bright cigarettes (Joly *et al.*, 1983; Vineis *et al.*, 1984, 1985; Benhamou *et al.*, 1985, 1987; DeStefani *et al.*, 1987).

The changing cigarettes — technical developments

The introduction of cigarettes with filter tips in North America and Europe around 1940 represents the first major change in the make-up of machine-made cigarettes. However, it was not until the first reports on smoking and lung cancer in the early 1950s that consumers demanded cigarettes with reduced 'tar'. In response, cigarettes with cellulose acetate filter tips were offered. These filter tips are usually 17-30-mm long and contain a few per cent of plasticizers such as glyceryl triacetate. In 1988, 96% of the cigarettes sold in the USA had filter tips; about half of them were 85-mm long and about one-third were 100-mm long (US Department of Agriculture, 1989). Similar developments were seen in other American countries, in Japan and in some parts of Europe, while in 1987 filter-tipped cigarettes in China accounted for only 26% and in the USSR, 27% (Anon., 1988).

The degree to which 'tar' and nicotine can be retained by conventional filter tips is limited to about 50%, primarily due to the fact that cigarette smokers will usually not accept a draw resistance above 140 mm (Kuhn & Klus, 1976). Apart from removing 'tar' and nicotine from the smoke, cellulose acetate can selectively remove up to 80% of certain hydrophilic, volatile smoke components, such as phenols and volatile *N*-nitrosamines (Wynder & Hoffmann, 1967; Brunnemann *et al.*, 1977).

The introduction of perforated filter tips around 1968 had a profound impact on the cigarette market (Norman, 1982). In general, such filter tips have one or more rows of perforation in the wrapper at the half-way point of the filter column. As a result, the smoke is diluted by air entering through the holes during puff-drawing without causing an increase in draw resistance. Enhancing the air dilution of the smoke stream by optimal perforation of the filter tip diminishes the velocity of the air that enters the burning cone. This, in turn, reduces the oxygen deficiency of certain zones in the burning cone, which results in the selective reduction of CO, nitrogen oxides and volatile aldehydes in these cigarettes (Newsome & Keith, 1965; Baker, 1984).

Even though cigarette length has increased from 70 mm to 85 mm, and even to 100 mm and 120 mm, the average weight of the tobacco in the typical US cigarette has decreased from 1300 mg in the 1940s to 750 mg in the 1980s (Norman, 1982). This is due mainly to

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the utilization in present-day cigarettes of tobacco material with higher filling power, namely reconstituted tobacco, tobacco ribs and expanded tobacco. Reconstituted tobacco sheets are made from tobacco dust and fines and from opened ribs. They can be prepared by slurry or paper-like processes. Expanded tobacco is obtained by a freeze-drying process (Wynder & Hoffmann, 1967; Perfetti, 1987).

The composition of cigarette smoke and its toxicity and carcinogenic potency are also very much affected by the tobacco type(s) used. The composition of the tobacco filler in cigarettes in different countries is primarily the result of traditional usage and availability of tobacco types. In the USA, the Federal Republic of Germany and Scandinavia, blends of the four major tobacco types are used; in China, flue-cured tobacco is the dominant type for cigarettes; while cigarettes made exclusively from flue-cured tobaccos are preferred in the UK and Finland. A large segment of cigarette smokers in France, Italy, North Africa and several Central and South American countries prefer black tobaccos.

Bright tobaccos contain generally high levels of reducing sugars (15-20% of dry weight) and carbohydrates but relatively lower amounts of di- and tricarboxylic acids (< 4%) and nitrate (< 0.1%), while burley and black tobaccos are low in reducing sugars (< 2%), relatively high in di- and tricarboxylic acids (> 10%) and high in nitrate (> 1%); this is especially true for the ribs. Oriental and Maryland tobaccos are minor components of cigarette blends because of their specific smoke flavours. Their leaves contain moderate amounts of reducing sugars (10-15%) and of di- and tricarboxylic acids (< 10%), while their nitrate content is low (Neurath & Ehmke, 1964; Tso, 1972). The nicotine concentration of the leaves depends on the variety chosen; however, bright, oriental and Maryland tobaccos contain less nicotine (< 2%) than burley and black tobaccos (Tso, 1972).

The composition of a typical blend currently formulated for US cigarettes is shown in Table 3 (the composition of expanded tobaccos is described by Perfetti, 1987). Other changes in the make-up of commercial cigarettes include the use of cigarette paper of higher porosity as well as reduction of the circumference of some cigarettes (DeBardeleben *et al.*, 1978; Owens, 1978). Together, all of these changes have led to a gradual decrease in the sales-weighted 'tar' and nicotine yields in the smoke of commercial US cigarettes (Figure 2).

The changing cigarette — effect on tumorigenicity of smoke

As discussed earlier, smokers of low-yield cigarettes tend to compensate for the reduced delivery of nicotine and perhaps other smoke components; however, they do not compensate fully. The 20-50% reduction in risk for lung cancer of long-term cigarette smokers supports the concept that low-yield cigarettes have reduced carcinogenic potential. The IARC monograph on tobacco smoking states: 'no substantial cause (or cofactor) has so far been identified that offers a plausible explanation for the observed magnitude of the reduction of risk for lung cancer, other than changes in the cigarette design which include reduction in tar content.' (IARC, 1986).

Whether other factors are indeed responsible for the reduced carcinogenic potential of the changed cigarette can at this time be evaluated only in laboratory studies. Concepts of 'less harmful' cigarettes have frequently been devised by investigators outside the industry

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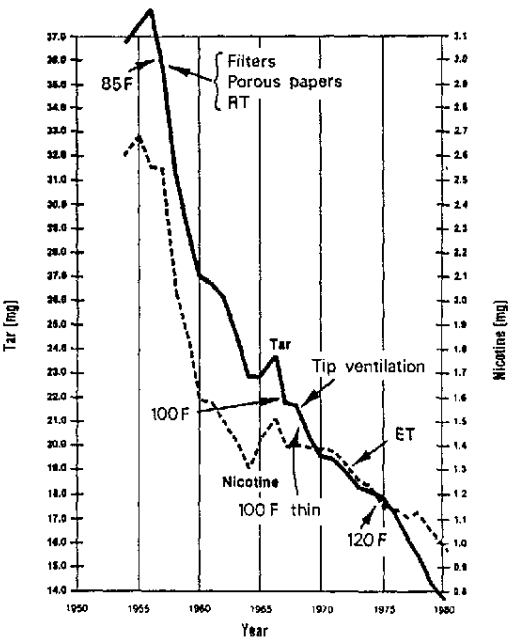
Table 2. Relative risk for lung cancer by type of cigarette smoked (filter *versus* nonfilter) in men

Reference	Type of study	Relative risk
Hawthorne & Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross & Gibson (1968)	Case-control	0.6
Wynder *et al.* (1970)	Case-control	0.6
Dean *et al.* (1977)	Case-control	0.5
Wynder & Stellman (1979)	Case-control	0.6-0.9[a]
Lubin (1984)	Case-control	0.6[b]

[a] Depending on number of cigarettes smoked daily
[b] Men who smoked only filter cigarettes

Figure 2. US sales-weighted average tar and nicotine yields (adapted from Norman, 1982)[a]



[a]RT, reconstituted tobacco; ET, expanded tobacco; F, cigarettes with filter tips; numbers, lengths of filter cigarettes in millimetres. Arrows denote years in which specific changes were first introduced

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Table 3. Composition of a typical US blend for cigarettes[a]

Component	%
Flue-cured leaf	32
Burley leaf	20
Maryland leaf	2
Oriental leaf	10
Cut, rolled stems	6
Reconstituted sheet	22
Dip casing	4
Flavours/humectants	4

[a] From Perfetti (1987)

(Wynder & Hoffmann, 1962; Hoffmann *et al.*, 1980). Various processes have been tested for their efficacy by initially analysing the smoke of the modified cigarettes for 'tar', nicotine, CO, benzo[*a*]pyrene and tobacco-specific *N*-nitrosamines (TSNA). When this analytical profile showed a reduction in the smoke yields, determinations of volatile aldehydes, volatile *N*-nitrosamines, cyanide, phenols and catechol were made. Experimental cigarettes with significantly changed analytical smoke profiles were then designated for evaluation of the toxicity and tumorigenic potential of their smoke. Such bioassays were done with 'tars' as well as with smoke itself (Wynder & Hoffmann, 1967; Dontenwill, 1974), as summarized in Table 4. Several of the modifications described here have been incorporated in the design of present-day low-yield cigarettes. Modifications in cigarette make-up have also led to the selective reduction of certain smoke constituents and have specifically contributed towards lowering the toxic and tumorigenic potential of cigarette smoke. The decline of benzo[*a*]pyrene levels in the smoke of a leading US non-filter cigarette as measured over 1958-79 is one indicator of selective reduction of a carcinogen; while 'tar' and nicotine in the smoke of this cigarette were reduced by 31% and 39%, the reduction in benzo[*a*]pyrene was from 36 to 16 ng/cigarette, i.e., 56% (Hoffmann *et al.*, 1980).

In evaluating preventive strategies that involve product modification, it is important to monitor not only specific indicators but also the overall chemical composition of the smoke of commercial cigarettes. Use of nitrate-rich tobaccos and ribs increases the potential for higher smoke yields of TSNA (Brunnemann *et al.*, 1983). Consequently, low-yield cigarettes can deliver higher amounts of carcinogenic TSNA than some plain cigarettes, as was recently shown for some cigarettes in the Federal Republic of Germany by Fischer *et al.* (1989). Another concern is the addition of flavouring agents to the tobacco of low-yield cigarettes (LaVoie *et al.*, 1985). These few citations underscore how important it is that nonindustrial scientists monitor new developments in the make-up of cigarettes.

Outlook

Future research and development will probably bring about new features in the design of commercial cigarettes. Plans have been announced for the marketing of filter cigarettes made with tobaccos from which the bulk of the nicotine has been removed by supercritical extraction with CO_2 (Grubbs & Howell, 1987). This development is potentially beneficial

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Table 4. Reductions in the biological activity of smoke from experimental cigarettes[a]

Method	Smoke constituents			Selective reduction in biological activity[b]		Remarks[c]
	'Tar'	Nicotine	Benzo[*a*]pyrene	Carcinogenicity	Tumour promotion	
Agricultural						
Tobacco type (bright–burley)[d]	+	+	+	+	+	Increase in TSNA
New cultivars	+	+	+	+	?	
Fertilization (nitrate)	+	+	+	+	?	Increase in TSNA
Tobacco processing						
Cut	±	±	±	±?	?	
Use of tobacco midribs	+	+	+	++	++	
Reconstituted tobacco sheets (*RTS*)[e]	+	+	+	++	±	Some RTS give high CO
RTS/paper process	++	+	+	++	±	
Expanded tobacco laminae	+	++	+	±?	±	
Expanded tobacco midribs	+	++	+	++	?	
Cigarette production						
Paper porosity	+	+	+	±	?	
Cellulose acetate filters	+	+	+	±	±	
Charcoal filters[f]	+	+	+	±	±	
Perforated filters	++	++	++	±	±	Smoker's compensation

[a] Adapted from Wynder & Hoffmann (1982). Methods known to be applied to commercial US cigarettes. Reductions: ++, > 50%; +, significant; ±?, questionable; ?, unknown

[b] Comparison of gram-to-gram 'tar' on mouse skin tests and/or smoke inhalation with hamsters

[c] TSNA, tobacco-specific *N*-nitrosamines

[d] Replacing bright with burley tobaccos

[e] Data given for RTS relate to those not made by the paper process

[f] Reductions in 'tar', nicotine, benzo[*a*]pyrene (and other nonvolatiles) and volatile *N*-nitrosamines are generally greater with cellulose acetate filters than with charcoal filters.

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in that it promises a selective reduction in the major habituating agent of tobacco and a precursor for carcinogenic TSNA. A recent attempt to market a modified cigarette that 'heats rather than burns tobacco' has not been accepted by consumers (R.J. Reynolds Tobacco Co., 1988).

Because large numbers of people continue to smoke cigarettes, development of less harmful cigarettes should not be rejected *per se*. One may agree with a recent editorial in the *New York Times* (Anon., 1989), which reads in part, 'Obviously, no smoking is better than smoking, but the best should not be the enemy of the good. There is a strong social case for encouraging manufacturers to develop safer cigarettes that will sell.'

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